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Asymptotic Behavior of Solutions to Single Loop Positive Feedback Systems

JAMES F. SELGRADE

Department of Mathematics, North Carolina State University, Raleigh, North Carolina 27650

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1. INTRODUCTION

Consider an n-dimensional system of ordinary differential equations of the form

$$\begin{aligned} \dot{x}_1 &= f(x_n) - \alpha_1 x_1, \\ \dot{x}_i &= x_{i-1} - \alpha_i x_i, \end{aligned} \qquad 2 \leqslant i \leqslant n, \tag{1}$$

where $0 < \alpha_i$ for $i = 1,..., n$. A system of this type provides a simple model for positive or negative feedback in biochemical control circuits [6, 7, 9, 11, 19, 21, 23, 24]. For example, the variables x_i, $1 \leqslant i \leqslant n - 1$, could represent the concentrations of a sequence of enzymes and x_n, the concentration of their substrate. For positive (or inductive) feedback, an increase in x_n causes an increase in the rate of production of x_1. For negative (or inhibitive) feedback, an increase in x_n causes a decrease in the rate of production of x_1.

Since chemical concentrations are nonnegative, it is reasonable (see Proposition 2.1) to restrict our attention to the positive orthant $\mathscr{H}$ in $\mathbf{R}^n$. Also we will deal only with the positive feedback system because of its monotonicity properties. Thus we assume f is a C^1 functions in a neighborhood of $\mathscr{H}$ satisfying the following conditions for $x_n \geqslant 0$:

(A1) $f(x_n) > 0$ if $x_n \neq 0$;

(A2) $f(x_n)$ is bounded; and

(A3) $f'(x_n) \geqslant 0$.

Assumption (A1) means that the presence of x_n causes the production of x_1. Assumption (A2) prevents the concentrations from becoming arbitrarily large as functions of time. Assumption (A3) makes the feedback inductive. Also we want a condition on the type of critical points of (1). So let ϕ denote the product of the α's, i.e., $\phi \equiv \alpha_1 \alpha_2 \cdots \alpha_n$.

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Define a function g for $x_n \geqslant 0$ by

$$g(x_n) \equiv f(x_n) - \phi x_n .$$

The zeroes of g determine the critical points of (1). We will make one of the following two assumptions:

(A4) g has k zeroes all simple, i.e., if $g(c) = 0$ then $g'(c) \neq 0$.

(D4) g has k zeroes $c_1, c_2, \ldots, c_k$ such that $g(x_n) \neq 0$ for $x_n \neq c_i$, $i = 1, \ldots, k$.

Assumption (A4) assures that the critical points are nondegenerate (see Theorem 4.1) and will be referred to as the "nondegenerate" case. Assumption (D4) allows the possibility of k isolated degenerate critical points. A critical point is called degenerate if it has a zero eigenvalue. Assumption (D4) will be referred to as the "degenerate" case although (D4) does not include all possible degenerate situations. Assumptions (A1) through (A4) are satisfied by the Griffith 3-dimensional model [7] where $f(x_3) = x_3^m/(1 + x_3^m)$ and by the Othmer–Tyson model [18, 24] where $f(x_n) = (1 + x_n^m)/(K + x_n^m)$, $K > 1$.

For (1) with assumptions (A1), (A2), (A3), and (A4) or (D4), we show that $\mathscr{H}$ is invariant for the positive time solution flow and that positive half-orbits in $\mathscr{H}$ are bounded. The critical points are situated on a half-line through the origin. In the nondegenerate case, the critical points alternate between asymptotically stable and unstable. Each unstable point has two orbits leaving it in opposite directions and each of these orbits is asymptotic to the adjacent stable critical point. For us, asymptotic refers only to positive time behavior and often will be written positively asymptotic for emphasis. In the degenerate case, there may be several adjacent unstable critical points. Additional information is obtained concerning the domains of attraction of the critical points. In particular, in dimensions 2 and 3 the stable manifolds of the unstable critical points separate $\mathscr{H}$ into regions of attraction. Thus the orbit of each point in $\mathscr{H}$ is asymptotic to some critical point.

Section 2 deals with notation and background. Section 3 establishes some basic results and properties for (1). Sections 4, 5, and 6 discuss the critical points, their domains of attraction and their stable and unstable manifolds. Section 7 handles the 2-dimensional case, $n = 2$. Section 8 deals with a special situation in the 3-dimensional case and contains crucial topological arguments. Section 9 and 10 finish the general 3-dimensional situation for the nondegenerate and degenerate cases.

2. Background and Basic Results

Let x or v denote a point in $\mathbf{R}^n$ and x_i or v_i will denote its ith component. If S is a subset of $\mathbf{R}^n$, let Int S, Bd S, and Cl S denote its topological interior, boundary, and closure, respectively. If S_1, $S_2 \subset \mathbf{R}^n$, define $S_1 \backslash S_2$ to be the set of points in S_1 that are not in S_2. Let θ denote the origin in $\mathbf{R}^n$. The positive orthant is given by $\mathscr{H}$, i.e.,

$$\mathscr{H} \equiv \{x \in \mathbf{R}^n : x_i \geqslant 0 \text{ for all } 1 \leqslant i \leqslant n\}.$$

Let G be a C^1 function from $\mathbf{R}^n$ to $\mathbf{R}^n$. In vector form an autonomous system of ordinary differential equations is denoted

$$\dot{x} = G(x), \tag{2}$$

where "$\cdot$" represents differentiation with respect to time $t \in \mathbf{R}$. G is called a *vector field.* The unique solution to (2) at time t with initial condition x will be written $x \cdot t$. The solution curve will be referred to as the orbit of flow of x. When discussing the components of a solution curve, the functional notation $x(t)$ is often more convenient than $x \cdot t$. We will assume solutions exist for all $t \geqslant 0$.

If T is a subset of $\mathbf{R}$ then define $x \cdot T \equiv \bigcup_{t \in T} x \cdot t$. Likewise, if $S \subset \mathbf{R}^n$ and $T \subset \mathbf{R}$, $S \cdot T \equiv \bigcup_{x \in S} x \cdot T$. S is *invariant* if $S \cdot t \subset S$ for all $t \in \mathbf{R}$ and S is *positively invariant* if $S \cdot t \subset S$ for all $t \geqslant 0$. Define the *ω-limit set* of S, $\omega(S)$, by

$$\omega(S) \equiv \bigcap_{t > 0} \mathrm{Cl}(S \cdot [t, \infty)).$$

A compact set $A \subset \mathbf{R}^n$ is called an *attractor* if A has a closed neighborhood $N \subset \mathbf{R}^n$ such that $\omega(N) = A$. A bounded set $S \subset \mathbf{R}^n$ is an *attracting region* if S is positively invariant and has a closed neighborhood N such that $\omega(N) \subset S$. Thus an attracting region contains an attractor. An attracting region which is rectangular will be called an *attracting box.* The *domain of attraction* of an attracting region S, dom S, is defined by

$$\operatorname{dom} S \equiv \{x \in \mathbf{R}^n : \omega(x) \subset S\}.$$

Note that the intersection of two attracting regions is an attracting region and the domain of attraction is an open set. If a critical point $\mathscr{C}$ of (2) is an attracting region then $\mathscr{C}$ is an attractor and $\mathscr{C}$ is called an *asymptotically stable* critical point.

From (2) we get a system of equations on $\mathbf{R}^n \times \mathbf{R}^n$ given by

$$\dot{x} = G(x), \qquad \dot{v} = DG(x)v, \tag{3}$$

where $(x, v) \in \mathbf{R}^n \times \mathbf{R}^n$ and $DG(x)$ is the derivative matrix of G at x. The vector space $x \times \mathbf{R}^n$ is called the *tangent space to* $\mathbf{R}^n$ *at* x, denoted $T_x\mathbf{R}^n$, and the solution flow to (3) is called the *tangent flow.* The second equation of (3) is referred to as the *linearized equations* of (2) and a solution will be written $v \cdot t$ or $v(t)$. The following result can be found in [8, p. 255];

PROPOSITION 2.1. *Suppose $x(t)$ is a nonconstant periodic solution to* (2). *If the trace of $DG(x(t))$ is negative for all $t \in \mathbf{R}$ then the periodic orbit has at least one characteristic root with norm less than* 1. *Thus there is a $k \geqslant 2$ and a k-dimensional C^1 manifold of solutions positively asymptotic to the periodic orbit, i.e., a k-dimensional stable manifold.*

The theory of differential inequalities is important for our analysis of (1). If $x, y \in \mathbf{R}^n$ then $x \leqslant y$ ($x < y$) if and only if $x_i \leqslant y_i$ ($x_i < y_i$) for $i = 1, 2, \ldots, n$. If G is a C^1 vector field on a domain $\mathscr{D} \subset \mathbf{R}^n$ and $z(t)$ is C^1 function from an interval (a, b) into $\mathscr{D}$, then $z(t)$ satisfies the differential inequality $\dot{z} \leqslant G(z)$ if $\dot{z}(t) \leqslant G(z(t))$ for all $t \in (a, b)$. The theory of differential inequalities goes back to Kamke [13] and is nicely presented in Coppel [2. pp. 27 ff.], where Theorem 2.2 can be found.

THEOREM 2.2. *Let G be a C^1 vector field on a neighborhood of the closure of a domain $\mathscr{D} \subset \mathbf{R}^n$ and let $\mathscr{D}$ be positively invariant under the solution flow of $\dot{x} = G(x)$. Suppose that $\partial G_i/\partial x_j \geqslant 0$ on $\mathscr{D}$ for all i and j, $i \neq j$. Let $x(t)$, $y(t)$, and $z(t)$ be C^1 from $[0, \infty)$ into $\mathscr{D}$. If $x(t)$ satisfies $\dot{x} = G(x)$. $y(t)$ satisfies $G(y) \leqslant \dot{y}$, $z(t)$ satisfies $\dot{z} \leqslant G(z)$, and if $z(0) \leqslant x(0) \leqslant y(0)$, then for all $t \in [0, \infty)$*

$$z(t) \leqslant x(t) \leqslant y(t).$$

In particular, if $y(t)$ satisfies $\dot{y} = G(y)$ and $x(0) \leqslant y(0)$, then $x(t) \leqslant y(t)$ for all $t \in [0, \infty)$.

Given $x \in \mathbf{R}^n$, the *positive* (*negative*) *cone of* x is the set of all points $y \in \mathbf{R}^n$ such that $x < y$ ($y < x$). The *cone of* x is the union of the positive and negative cones of x. Two distinct points $x \neq y$ are said to be *related* if $x \leqslant y$ or $y \leqslant x$, i.e., y is in the closure of the cone of x and, likewise, x is in the closure of the cone of y. With the assumptions of Theorem 2.2, the last sentence of the theorem asserts that being related is invariant under the positive-time flow of $\dot{x} = G(x)$. In fact we need the stronger conclusion of Theorem 2.2 for the following important lemma.

LEMMA 2.3. *Suppose G satisfies the hypotheses of Theorem 2.2. Let $x(t)$ denote the solution to $x = G(x)$ with $x(0) = p \in \mathscr{D}$. If $\theta \leqslant G(p)$ then for each i, $1 \leqslant i \leqslant n$, the function $x_i(t)$ is nondecreasing for $t \geqslant 0$. If $G(p) \leqslant \theta$ then for each i, $1 \leqslant i \leqslant n$, the function $x_i(t)$ is nonincreasing for $t \geqslant 0$. In either case, if the positive orbit of p is bounded then $\omega(p)$ is one critical point.*

Proof. Suppose $\theta \leqslant G(p)$. Define $z(t) \equiv p$ for $t \geqslant 0$. We have for $t \geqslant 0$

$$\dot{z}(t) = \theta \leqslant G(p) = G(z(t)).$$

Hence Theorem 2.2 implies that for all $t \geqslant 0$

$$p = z(t) \leqslant x(t) = p \cdot t. \tag{4}$$

Fixing $t > 0$ in (4) and appealing to the last assertion of Theorem 2.2, we get that for all $s \geqslant 0$

$$p \cdot s \leqslant (p \cdot t) \cdot s.$$

But $(p \cdot t) \cdot s = p \cdot (t + s)$. Hence the components of the positive orbit of p are nondecreasing functions of time.

If $G(p) \leqslant \theta$ then define $y(t) \equiv p$ for $t \geqslant 0$. Thus for $t \geqslant 0$

$$G(y(t)) = G(p) \leqslant \theta = \dot{y}(t).$$

Theorem 2.2 gives that for all $t \geqslant 0$

$$p \cdot t = x(t) \leqslant y(t) = p.$$

As above, it follows that the components of the positive orbit of p are nonincreasing functions of time.

In either case, if the positive orbit of p is bounded, each component function converges at $t \to \infty$. Thus the positive orbit of p is asymptotic to one critical point.

If either of the properties in Lemma 2.3 hold, the orbit of p is said to be *monotone*. This monotonicity will be used to find attracting regions in Section 5.

Finally, we state a classical matrix theory result. An $n \times n$ matrix A is *positive* if all its entries are positive. This next result is due to Perron and can be found in Gantmacher [3, p. 53].

THEOREM 2.4. *A positive matrix A always has a positive eigenvalue μ (called the principal eigenvalue of A) that is a simple root of the characteristic equation and exceeds the moduli of all other eigenvalues of A. To μ there corresponds an eigenvector (called the principal eigenvector of A) with positive components.*

3. BASIC RESULTS FOR (1)

In this section we establish some basic properties of (1) and apply several results in the last section to (1).

PROPOSITION 3.1. *If* (1) *satisfies* (A1) *then* Int $\mathscr{H}$ *is positively invariant.*

Proof. Take $x \in \operatorname{Int} \mathscr{H}$. Using variation of parameters we get the following equations in the components of x:

$$
\begin{aligned}
x_1(t) &= x_1(0)\exp(-\alpha_1 t) + \int_0^t \exp(-\alpha_1(t-s))\, f(x_n(s))\, ds, \\
x_i(t) &= x_i(0)\exp(-\alpha_i t) + \int_0^t \exp(-\alpha_i(t-s))\, x_{i-1}(s)\, ds, \qquad 2 \leqslant i \leqslant n.
\end{aligned}
\tag{5}
$$

Assume that the positive orbit of x leaves $\operatorname{Int} \mathscr{H}$. Then there is a first time $t^* > 0$ such that the orbit of $x(t)$ meets $\operatorname{Bd} \mathscr{H}$. Thus at least one component of $x(t^*)$, say $x_k(t^*)$, is zero; and $x_j(t) > 0$ for all j and t, $0 \leqslant t < t^*$. From (5) it follows that $x_k(t^*) > 0$ since $\int_0^{t^*} \exp(-\alpha_k(t^* - s))\, x_{k-1}(s)\, ds > 0$ for $k > 1$ and $\int_0^{t^*} \exp(-\alpha_1(t^* - s))\, f(x_n(s))\, ds > 0$ for $k = 1$. This contradiction implies that $x(t) \in \operatorname{Int} \mathscr{H}$ for all $t \geqslant 0$.

COROLLARY 3.2. *If* (1) *satisfies* (A1) *then* $\mathscr{H}$ *is positively invariant. In fact,* $(\mathscr{H}\backslash\theta) \cdot t \subset \operatorname{Int} \mathscr{H}$ *for all* $t > 0$; *and, if* $f(0) \neq 0$, *then* $\mathscr{H} \cdot t \subset \operatorname{Int} \mathscr{H}$ *for all* $t > 0$.

Proof. The first statement follows from Proposition 3.1 using continuity of solutions in initial conditions.

For the second statement take $x \in \mathscr{H}\backslash\theta$. Then some component $x_i \neq 0$. Since $x_{i-1}(t) \geqslant 0$ $i \neq 1$ and $f(x_n(t)) \geqslant 0$ for all $t \geqslant 0$, from (5) we have $x_i(t) > 0$ for all $t > 0$. But then (5) implies that $x_{i+1}(t) > 0$ for all $t > 0$. Continue in this way to show all components of $x(t)$ are positive for $t > 0$. If $f(0) \neq 0$, start this procedure by showing $x_1(t) > 0$ for $t > 0$.

PROPOSITION 3.3. *If* (1) *satisfies* (A2) *then positive orbits of points in* $\mathscr{H}$ *are bounded.*

Proof. Let M be the bound for f. Take $x \in \mathscr{H}$. From (5) it follows that for $t \geqslant 0$

$$x_1(t) \leqslant x_1(0) + (M/\alpha_1).$$

Recursively define

$$M_0 \equiv M \qquad \text{and} \qquad M_i \equiv x_i(0) + (M_{i-1}/\alpha_i) \qquad \text{for} \quad 1 \leqslant i \leqslant n.$$

Then (5) implies that M_i is a bound for $x_i(t)$, $t \geqslant 0$. This completes the proof.

The vector field of (1) will be denoted by $F(x)$ and the Jacobian matrix of F at x is

$$
DF(x) = \begin{pmatrix}
-\alpha_1 & 0 & \cdots & & f'(x_n) \\
1 & -\alpha_2 & 0 & \cdots & 0 \\
0 & 1 & -\alpha_3 & \cdots & 0 \\
\vdots & & & & \vdots \\
0 & & & 1 & -\alpha_n
\end{pmatrix}.
\tag{6}
$$

In component form, the linearized equations of (1) are written

$$\begin{aligned} \dot{v}_1 &= f'(x_n(t))\, v_n - \alpha_1 v_1, \\ \dot{v}_i &= v_{i-1} - \alpha_i v_i, \end{aligned} \qquad 2 \leqslant i \leqslant n. \tag{7}$$

Notice from (6) the trace of $DF(x)$ is negative so at each critical point $\mathscr{C}$ of (1) $DF(\mathscr{C})$ has at least one eigenvalue with negative real part. Thus $\mathscr{C}$ has at least a 1-dimensional stable manifold. And Proposition 2.1 implies that each nonconstant periodic orbit of (1) has at least a 2-dimensional stable manifold.

With the (A3) assumption the off-diagonal terms of $DF(x)$ are nonnegative for all $x \in \mathscr{H}$. Hence Theorem 2.2 applies with $\mathscr{D} = \operatorname{Int} \mathscr{H}$; and so the positive-time flow of (1) preserves inequalities in $\operatorname{Int} \mathscr{H}$. We are forced to choose $\mathscr{D} = \operatorname{Int} \mathscr{H}$ instead of a neighborhood of $\mathscr{H}$ because the biochemical examples may not satisfy $f'(x_n) \geqslant 0$ if $x_n < 0$. But this causes no problem because Corollary 3.2 implies that all orbits, except possibly θ, starting on $\operatorname{Bd} \mathscr{H}$ immediately enter $\operatorname{Int} \mathscr{H}$.

Henceforth, we tactily assume (A1), (A2), and (A3) and restrict our attention to the flow of (1) in $\mathscr{H}$.

4. Critical Points

Finding the critical points of (1) can be reduced to solving for the non-negative zeroes of $g(x_n) = f(x_n) - \phi x_n$. Note that $g(x_n) \to -\infty$ as $x_n \to \infty$ since $f(x_n)$ is bounded. Since $f(0) \geqslant 0$, we have $g(0) \geqslant 0$ and equality holds if and only if $f(0) = 0$. Assuming (A4) or (D4), we arrange the nonnegative zeroes of g in increasing order $c_1 < c_2 < \cdots < c_k$. Make the following recursive definition:

$$\phi_0 \equiv \phi \qquad \text{and} \qquad \phi_i \equiv \phi_{i-1}/\alpha_i \qquad \text{for} \quad 1 \leqslant i \leqslant n.$$

Note that $\phi_n = 1$. The critical points of (1) are multiples of the point $\Phi \equiv (\phi_1, \phi_2, \ldots, \phi_n) \in \mathbf{R}^n$, i.e., they can be ordered $\mathscr{C}_1 < \mathscr{C}_2 < \cdots < \mathscr{C}_k$, where $\mathscr{C}_i = c_i \Phi$, $1 \leqslant i \leqslant k$. Hence these critical points lie along the half-line $\mathscr{L} \equiv \{c\Phi : c \geqslant 0\}$. And $\mathscr{C}_1$ is the origin if and only if $f(0) = 0$. The sign of g determines which way the vector field F is pointing along the half-line $\mathscr{L}$. For $c > 0$, since $\alpha_i \phi_i = \phi_{i-1}$, we have

$$F(c\Phi) = (f(c) - \phi c, c\phi_1 - \alpha_2 c\phi_2, \ldots, c\phi_{n-1} - \alpha_n c\phi_n) = (g(c), 0, \ldots, 0).$$

If $g(c) > 0$ then $F(c\Phi) \geqslant \theta$; and, if $g(c) < 0$ then $F(c\Phi) \leqslant \theta$. This will be useful for finding attracting regions in Section 5.

The function g carries some additional information about the critical points. Since $g'(x_n) = f'(x_n) - \phi$, it is easy to compute

$$\det DF(\mathscr{C}_i) = (-1)^{n+1} g'(c_i), \qquad 1 \leqslant i \leqslant k. \tag{8}$$

THEOREM 4.1. *If* (1) *satisfies* (A4) *then each critical point* $\mathscr{C}_i$, $1 \leqslant i \leqslant k$, *is nondegenerate. In fact, if* $g'(c_i) > 0$ *then* $\mathscr{C}_i$ *has at least a* 1*-dimensional unstable manifold.*

Proof. Since $g'(c_i) \neq 0$, (8) asserts that $DF(\mathscr{C}_i)$ has no zero eigenvalue. If $g'(c_i) > 0$ then it is clear from (8) that $DF(\mathscr{C}_i)$ has a positive real eigenvalue and hence at least a 1-dimensional unstable manifold.

Next we use the Perron theorem to say more about the stability of the critical points. Consider the linearized equations (7) at a critical point $\mathscr{C}_i$. Notice that (7) is a special case of (1) where the nonlinear term in (1) is replaced by the linear term $f'(c_i)\, v_n$. If $f'(c_i) \neq 0$ then $f'(c_i)\, v_n > 0$ when $v_n > 0$. Thus (7) satisfies (A1). The matrix $\exp(tDF(\mathscr{C}_i))$ is the fundamental matrix of (7) with the identity as initial condition. So Corollary 3.2 gives that, for nonzero $v \geqslant \theta$ and for $t > 0$,

$$\theta < \exp(tDF(\mathscr{C}_i))v. \tag{9}$$

Hence $\exp(tDF(\mathscr{C}_i))$ is a positive matrix. Theorem 2.4 now gives the following lemma:

LEMMA 4.2. *If* $f'(c_i) \neq 0$ *then* $\exp(tDF(\mathscr{C}_i))$ *is a positive matrix for each* $t > 0$. *And* $\exp(DF(\mathscr{C}_i))$ *has a unique positive eigenvalue* μ *with maximum modulus and a corresponding positive eigenvector.*

THEOREM 4.3. *Let* $\mathscr{C}_i$ *be a critical point of* (1). *Then one of the following is true*:

(a) *all eigenvalues of* $DF(\mathscr{C}_i)$ *have negative real parts.*

(b) *there is a unique nonnegative eigenvalue of* $DF(\mathscr{C}_i)$ *having maximal real part and the corresponding eigenvector lies in the positive cone.*

Proof. If $f'(c_i) = 0$ then $DF(\mathscr{C}_i)$ is lower triangular with all negative eigenvalues; so (a) holds. If $f'(c_i) \neq 0$ then Lemma 4.2 gives (a) or (b). If $\mu > 1$ then (b) hold. If $\mu = 1$ then (b) holds and the remaining $n - 1$ eigenvalues of $DF(\mathscr{C}_i)$ have negative real parts. If $\mu < 1$ then (a) is true.

In the next section we show that if $g'(c_i) < 0$ then (a) is true. Hence, in the nondegenerate case, the sign of $g'(c_i)$ distinguishes between the asymptotic stability and instability of the critical point $\mathscr{C}_i$.

5. Attracting Boxes and Domains of Attraction

First we determine the asymptotic behavior of boxes with diagonals along the half-line $\mathscr{L}$ and with faces parallel to the coordinate planes. For $0 \leqslant r_1 < r_2 \leqslant \infty$ define the box,

$$B(r_1, r_2) \equiv \{x \in \mathscr{H}: r_1\Phi \leqslant x \leqslant r_2\Phi\}.$$

We use Lemma 2.3 to study the orbits of the two corner points of these boxes, on $\mathscr{L}$. Unless stated otherwise, the results in the rest of this paper assume that (1) satisfies either (A4) or (D4).

Lemma 5.1. *Let $c > 0$. If $g(c) < 0$ then the positive orbit of the point $c\Phi$ is monotone and asymptotic to the largest critical point less than $c\Phi$. If $g(c) > 0$ then the positive orbit of $c\Phi$ is monotone and asymptotic to the smallest critical point greater than $c\Phi$.*

Proof. If $g(c) < 0$ then $F(c\Phi) \leqslant \theta$. Also $c\Phi \in \operatorname{Int} \mathscr{H}$. Thus Lemma 2.3 asserts that the positive orbit of $c\Phi$ is monotone and $\omega(c\Phi)$ is a critical point less than $c\Phi$. Let $\mathscr{C}_i$ denote the largest critical point less than $c\Phi$. Since the flow of (1) preserves inequalities, we have $\mathscr{C}_i \leqslant (c\Phi) \cdot t$ for all $t \geqslant 0$. Hence $\omega(c\Phi) = \mathscr{C}_i$.

The second assertion follows similarly from Lemma 2.3.

We argue that Lemma 5.1 gives the asymptotic behavior of all points on $\mathscr{L}$, although $\mathscr{L}$ is not invariant. If $c\Phi$ is between critical points then its orbit is asymptotic to the larger or smaller critical point depending on the sign of $g(c)$. If $c\Phi$ is greater than the largest critical point $\mathscr{C}_k$, then $g(c) < 0$; so the orbit of $c\Phi$ is asymptotic to $\mathscr{C}_k$. If $\theta \leqslant c\Phi < \mathscr{C}_1$ then $g(c) > 0$ because $g(0) > 0$. In this case, if $c \neq 0$ then it follows directly from Lemma 5.1 that the orbit of $c\Phi$ is asymptotic to $\mathscr{C}_1$. If $c = 0$, Corollary 3.2 implies that $\theta \cdot t \in \operatorname{Int} \mathscr{H}$ for all $t > 0$. Fix a $t > 0$; there is some $c' > 0$ so that $c'\Phi \leqslant \theta \cdot t \leqslant \mathscr{C}_1$ and $g(c') > 0$. Thus the orbit of θ is asymptotic to $\mathscr{C}_1$ since the orbit of $c'\Phi$ is.

Lemma 5.2. *Consider the critical point $\mathscr{C}_i$. If $\mathscr{C}_i = \theta$ then $B(0, c_k)$ is an attracting box with $\mathscr{H} \subset \operatorname{dom} B(0, c_k)$. If $\mathscr{C}_i \neq \theta$ but $g(c) > 0$ for $c_{i-1} < c < c_i$. ($c_{i-1} = 0$ if $i = 1$), then $B(c_i, c_k)$ is an attracting box with* $\operatorname{Int} B(c_{i-1}, \infty) \subset \operatorname{dom} B(c_i, c_k)$.

Proof. Let $\mathscr{C}_i = \theta$. If $z \in B(0, c_k)$ then $\theta \leqslant z \leqslant \mathscr{C}_k$. Thus $\theta \leqslant z \cdot t \leqslant \mathscr{C}_k$ for $t \geqslant 0$; so $B(0, c_k)$ is positively invariant. For $c' > c_k$, $g(c') < 0$ since $g(x_n) \to -\infty$ as $x_n \to \infty$. Lemma 5.1 asserts that the orbit of $c'\Phi$ is monotone and asymptotic to $\mathscr{C}_k$. Hence $\omega(B(0, c')) \subset B(0, c_k)$, and so $B(0, c_k)$ is an attracting box with $\mathscr{H} \subset \operatorname{dom} B(0, c_k)$.

If $\mathscr{C}_i \neq \theta$ and $g(c) > 0$ for $c_{i-1} < c < c_i$, then the orbit of $c\Phi$ is monotone and asymptotic to $\mathscr{C}_i$ by Lemma 5.1. For $c' > c_k$, the orbit of $c'\Phi$ is monotone and asymptotic to $\mathscr{C}_k$. Thus $\omega(B(c, c')) \subset B(c_i, c_k)$. So $B(c_i, c_k)$ is an attracting box with $\operatorname{Int} B(c_{i-1}, \infty) \subset \operatorname{dom} B(c_i, c_k)$.

Remark. In Lemma 5.2 if $i = 1$ and $\mathscr{C}_1 \neq \theta$ then $B(0, \infty) = \mathscr{H} \subset \operatorname{dom} B(c_1, c_k)$ by Corollary 3.2.

LEMMA 5.3. *Consider the critical point $\mathscr{C}_i$ and let $c_{i+1} = \infty$ if $i = k$. If $g(c) < 0$ for $c_i < c < c_{i+1}$ then $B(0, c_i)$ is an attracting box with* $\operatorname{Int} B(0, c_{i+1}) \subset \operatorname{dom} B(0, c_i)$.

Proof. Clearly $B(0, c_i)$ is positively invariant. For c, $c_i < c < c_{i+1}$, Lemma 5.1 gives that the orbit of $c\Phi$ is monotone and asymptotic to $\mathscr{C}_i$. Thus $\omega(B(0, c)) \subset B(0, c_i)$, and so $B(0, c_i)$ is an attracting box with $\operatorname{Int} B(0, c_{i+1}) \subset \operatorname{dom} B(0, c_i)$.

THEOREM 5.4. *Consider $\mathscr{C}_i \leqslant \mathscr{C}_j$. Let $c_{i-1} = 0$ if $i = 1$ and $c_{j+1} = \infty$ if $j = k$. If $g(c) > 0$ for $c_{i-1} < c < c_i$ (this condition is not needed if $\mathscr{C}_i = \theta$) and $g(c) < 0$ for $c_j < c < c_{j+1}$, then $B(c_i, c_j)$ is an attracting box with* $\operatorname{Int} B(c_{i-1}, c_{j+1}) \subset \operatorname{dom} B(c_i, c_j)$. *In particular, if $\mathscr{C}_i = \mathscr{C}_j$ then $\mathscr{C}_i$ is an asymptotically stable critical point.*

Proof. From Lemma 5.2, we have that $B(c_i, c_k)$ is an attracting box with $\operatorname{Int} B(c_{i-1}, \infty) \subset \operatorname{dom} B(c_i, c_k)$. From Lemma 5.3, we have $B(0, c_j)$ is an attracting box with $\operatorname{Int} B(0, c_{j+1}) \subset \operatorname{dom} B(0, c_j)$. Thus $B(c_i, c_j) = B(c_i, c_k) \cap B(0, c_j)$ is an attracting box with $\operatorname{Int} B(c_{i-1}, c_{j+1}) \subset \operatorname{dom} B(c_i, c_j)$. If $\mathscr{C}_i = \mathscr{C}_j$ then $\mathscr{C}_i = B(c_i, c_j)$ is an attractor and, hence, asymptotically stable. Note that if $\mathscr{C}_i = \mathscr{C}_j = \theta$ then θ is an attractor in $\mathscr{H}$ although θ may not be an attractor in $\mathbf{R}^n$.

COROLLARY 5.5. *Suppose $\mathscr{C}_i$ is nondegenerate. Then $\mathscr{C}_i$ is asymptotically stable if and only if $g'(c_i) < 0$.*

Proof. Sufficiency follows from Theorem 5.4 and necessity, from Theorem 4.1.

COROLLARY 5.6. *Suppose* (1) *satisfies* (A4). *If $g(0) > 0$ then $B(c_1, c_k)$ is an attracting box with $\mathscr{H} \subset$* dom *$B(c_1, c_k)$ and the number of critical points k must be odd. If $g(0) = 0$ then $\mathscr{C}_1$ is the origin; and*

(a) *if $g'(0) < 0$ then $B(0, c_k)$ is an attracting box with $\mathscr{H} \subset$* dom *$B(0, c_k)$ and k is odd, or*

(b) *if $g'(0) > 0$ then $B(c_2, c_k)$ is an attracting box with $\mathscr{H}\backslash\theta \subset$* dom *$B(c_2, c_k)$ and the number of critical points in $B(c_2, c_k)$ is odd.*

Corollary 5.6 reduces the study of the asymptotic behavior in the nondegenerate case to studying asymptotic behavior in an attracting box which

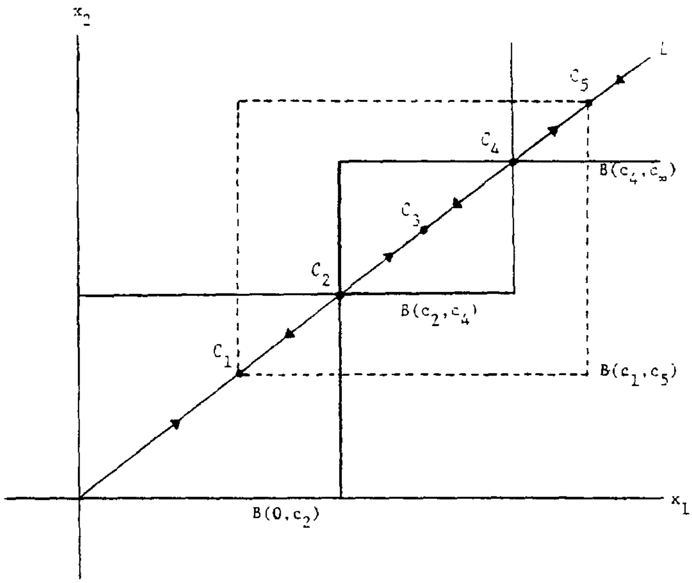

FIGURE 1

contains an odd number of critical points. Hence we may assume that $\theta < \mathscr{C}_1$ and that the odd subscripted critical points are asymptotically stable and the even subscripted critical points are unstable. If $\mathscr{C}_i$ is stable then each point in Int $B(c_{i-1}, c_{i+1})$ is asymptotic to $\mathscr{C}_i$. These boxes are situated along the line $\mathscr{L}$ and separated from one another by the unstable critical points. Also $B(c_1, c_k)$ is an attracting box with $\mathscr{H} \subset$ dom $B(c_1, c_k)$. Figure 1 illustrates this when $n = 2$ and $k = 5$. The arrows in Fig. 1 denote the direction of the vector field along $\mathscr{L}$. The degenerate case is more complicated because there may be several adjacent unstable critical points

6. Stable and Unstable Manifolds of Critical Points

Let $\mathscr{C}_i$ be a critical point of (1). From Theorem 4.3 we know that all eigenvalues of $DF(\mathscr{C}_i)$ have negative real parts (we call such a $\mathscr{C}_i$ *strongly stable*) or there is a nonnegative eigenvalue μ of $DF(\mathscr{C}_i)$ exceeding the real part of all other eigenvalues and having an eigenvector lying in the positive cone at $\mathscr{C}_i$. In the latter case either $\mu > 0$ and we call $\mathscr{C}_i$ *strongly unstable*, or $\mu = 0$ and we call $\mathscr{C}_i$ *neutral*. If $\mu > 0$ there is a unique 1-dimensional unstable manifold tangent to the principal eigendirection at $\mathscr{C}_i$. This unstable manifold is composed to two orbits leaving $\mathscr{C}_i$. One orbit lies in $B(c_i, c_{i+1})$ and is positively asymptotic to $\mathscr{C}_{i+1}$; and the other orbit lies in $B(c_{i-1}, c_i)$ and is positively asymptotic to $\mathscr{C}_{i-1}$. Hence

$g(c) > 0$ for $c_i < c < c_{i+1}$ and $g(c) < 0$ for $c_{i-1} < c < c_i$. If $\mu = 0$ then all other eigenvalues of $DF(\mathscr{C}_i)$ have negative real parts. Thus there is a 1-dimensional center manifold (not necessarily unique) tangent to the principal eigendirection at $\mathscr{C}_i$. This manifold is composed of two orbits, one in $B(c_i, c_{i+1})$ and the other in $B(c_{i-1}, c_i)$, and the direction of motion for each orbit is determined by the sign of g between c_i and c_{i+1} and between c_{i-1} and c_i. For example, if $g(c) < 0$ for $c_i < c < c_{i+1}$, then the orbit in $B(c_i, c_{i+1})$ leaves $\mathscr{C}_{i+1}$ and is positively asymptotic to $\mathscr{C}_i$. Hence, in case (b) of Theorem 4.3, the sign of g near c_i determines the motion of orbits in the principal eigendirection at $\mathscr{C}_i$.

If $\mathscr{C}_i$ is strongly unstable or neutral, then $\mathscr{C}_i$ has a stable manifold because the trace of $DF(\mathscr{C}_i)$ is negative. Let M_i denote the unique stable manifold corresponding to the set of all eigenvalues of $DF(\mathscr{C}_i)$ with negative real parts. M_i in a C^1 manifold immersed in Int $\mathscr{H}$ and tangent at $\mathscr{C}_i$ to the eigenspace $\mathscr{C}_i \times E_i^s \subset \mathbf{R}^n \times \mathbf{R}^n$ determined by all eigenvalues of $DF(\mathscr{C}_i)$ with negative real parts. All orbits in M_i are positively asumptotic to $\mathscr{C}_i$.

THEOREM 6.1. *Let $\mathscr{C}_i$ be a critical point of* (1). *Then $\mathscr{C}_i$ is asymptotically stable or unstable. $\mathscr{C}_i$ is unstable if and only if either $g(c) < 0$ for $c_{i-1} < c < c_i$ or $g(c) > 0$ for $c_i < c < c_{i+1}$. Assume $c_{i-1} = 0$ if $i = 1$ and $c_{i+1} = \infty$ if $i = k$.*

Proof. We need consider only a neutral point of $\mathscr{C}_i$. $\mathscr{C}_i$ has a 1-dimensional center manifold and an $(n - 1)$-dimensional stable manifold M_i. Following from the equivalency extension of Palis and Takens [20], the flow in a neighborhood of $\mathscr{C}_i$ is equivalent (two flows are *equivalent* if there is a homeomorphism taking orbits onto orbits) to the product flow on the Cartesian product of the center manifold and the stable manifold. The orbits on M_i are asymptotic to $\mathscr{C}_i$; and the flow on the center manifold is determined by g near c_i. Thus, if $g(c) > 0$ for $c_{i-1} < c < c_i$ and $g(c) < 0$ for $c_i < c < c_{i+1}$, then the flow on the center manifold must be positively asymptotic to $\mathscr{C}_i$. Hence $\mathscr{C}_i$ is asymptotically stable. If either $g(c) < 0$ for $c_{i-1} < c < c_i$ or $g(c) > 0$ for $c_i < c < c_{i+1}$ then at least one orbit on the center manifold of $\mathscr{C}_i$ is positively asymptotic to another critical point. Thus $\mathscr{C}_i$ is unstable.

Next we say more about how M_i lies in Int $\mathscr{H}$.

LEMMA 6.2. *Let $\mathscr{C}_i$ be an unstable critical point of* (1). *Then the vector space E_i^s determined by all eigenvalues of $DF(\mathscr{C}_i)$ with negative real parts contains no related points. In particular, if $v \neq \theta \in \mathbf{R}^n$ and either $\theta \leqslant v$ or $v \leqslant \theta$, then $v \notin E_i^s$.*

Proof. Suppose there is a $v \neq \theta$ such that $\theta \leqslant v$ and $v \in E_i^s$. Lemma 4.2 states that the fundamental matrix $\exp(tDF(\mathscr{C}_i))$ *is positive* for $t > 0$. Hence, for $t > 0$,

$$\theta < \exp(tDF(\mathscr{C}_i))v.$$

But E_i^s is invariant under $\exp(tDF(\mathscr{C}_i))$, so E_i^s intersects the positive and negative cones at $\mathscr{C}_i$. Thus M_i intersects both Int $B(c_{i-1}, c_i)$ and Int $B(c_i, c_{i+1})$. From Theorem 6.1 we know that either $g(c) < 0$ for $c_{i-1} < c < c_i$ or $g(c) > 0$ for $c_i < c < c_{i+1}$. So either Int $B(c_{i-1}, c_i)$ or Int $B(c_i, c_{i+1})$ consists of points none of whose orbits are positively asymptotic to $\mathscr{C}_i$. This contradiction and the fact that E_i^s is a linear space completes the proof.

The following theorem should be true without any restriction on the codimension of M_i but the prove given here requires the restriction.

THEOREM 6.3. *Let $\mathscr{C}_i$ be an unstable critical point with an $(n - 1)$-dimensional stable manifold M_i. Then M_i contains no related points.*

Proof. The subsequent argument uses Lemma 6.2 to obtain the result locally at $\mathscr{C}_i$ and the result for all points of M_i follows from the fact that being related is invariant under the positive-time flow of (1).

Lemma 6.2 implies that the normal vector to M_i at $\mathscr{C}_i$ can be chosen to lie in the positive cone at $\mathscr{C}_i$. Using basic stable manifold theory [12, 18, 22], it follows that a small neighborhood of $\mathscr{C}_i$ in M_i, call it M_i^{loc}, is diffeomorphic to an $(n - 1)$-disk. Also M_i^{loc} is positively invariant. Using the continuity of the tangent space to M_i and shrinking M_i^{loc} if necessary, we assume that the normal vector at each point of M_i^{loc} has all positive components. Appealing to the implicit function theorem and shrinking M_i^{loc} again, we assume that M_i^{loc} is the graph of a C^1 function h of the first $n - 1$ coordinates with domain a convex set K in $\mathbf{R}^{n-1}$. The normal vector at each point of M_i^{loc} can be written $(-\nabla h(x), 1)$ where $x \in K$ and $\nabla h(x)$ denotes the gradient of h at x. Since this normal vector is positive, for all $x \in K$ we have

$$\nabla h(x) < \theta. \tag{10}$$

Suppose M_i^{loc} contains two related points, i.e., there are points $w, y \in K$ such that $(y, h(y)) \leqslant (w, h(w))$ and $(w, h(w)) \neq (y, h(y))$. The mean value theorem for functions of $n - 1$ variables asserts that

$$h(w) - h(y) = \sum_{i=1}^{n-1} (w_i - y_i)\, \partial h(p)/\partial x_i \tag{11}$$

for some $p \in K$. The left-hand side of (11) is nonnegative and the right-hand side of (11) is nonpositive by (10). But both sides of (11) cannot be zero. This contradiction implies that M_i^{loc} contains no related points.

For any two points of M_i there is a large time such that after that time the orbits of both points are in M_i^{loc}. If the two points were related, they would produce two related points in M_i^{loc}. But this is impossible. Hence the theorem is proved.

As a consequence of Theorem 6.2 we know that each line perpendicular to a coordinate hyperplane may intersect M_i at most once. Hence there is a "$1 - 1$" projection of M_i into each coordinate hyperplane and so M_i can be considered the graph of a function of any group of $n - 1$ variables.

COROLLARY 6.4. *If $\mathscr{C}_i$ is a neutral point then M_i contains no related points.*

7. THE TWO-DIMENSIONAL CASE

In this section we assume that (1) is a 2-dimensional system, i.e., $n = 2$. From the Poincaré–Bendixson theorem [8, p. 151], we know that an orbit in $\mathscr{H}$ is asymptotic to a critical point or a periodic orbit. The following result eliminates the latter.

LEMMA 7.1. *$\mathscr{H}$ contains no nonconstant periodic solutions of* (1).

Proof. From Corollary 3.2 we need consider only Int $\mathscr{H}$. Suppose p is a point on a nonconstant periodic orbit in Int $\mathscr{H}$ of minimal period τ. Since the orbit is a C^1 curve, either the horizontal line or the vertical line through p intersects the periodic orbit at another point q. Without loss of generality assume $p \leqslant q$. Since inequalities are preserved by the flow, for all $t \geqslant 0$

$$p \cdot t \leqslant q \cdot t.$$

There is an s, $0 < s < \tau$, such that $q = p \cdot s$. Thus $q = p \cdot s \leqslant q \cdot s$ and for all $t \geqslant 0$

$$q \cdot t \leqslant q \cdot (s + t).$$

In particular, for each positive integer j

$$q \cdot (js) \leqslant q \cdot ((j + 1)s).$$

Hence the sequence of points $q \cdot (js)$, $j = 1, 2, 3,\ldots$, is nondecreasing and converges to a point of period s as $j \to \infty$. This contradiction implies that there are no constant periodic orbits in Int $\mathscr{H}$.

Notice that this result follows from the Bendixson critèrion [15, p. 227] since the trace of $DF(x)$ is constant on $\mathscr{H}$. But the proof given here works for any 2-dimensional system where inequalities are preserved.

Theorem 6.1, Lemma 7.1, and the Poincaré–Bendixson theorem now give;

THEOREM 7.2. *The orbit of each point in $\mathscr{H}$ is positively asymptotic to some critical point. If $\mathscr{C}_i$ is an unstable critical point, its stable manifold M_i is 1-dimen-*

sional. Each M_i separates $\mathscr{H}$ into regions of orbits positively asymptotic to $\mathscr{C}_{i-1}$, $\mathscr{C}_i$, or $\mathscr{C}_{i+1}$ depending on the sign of g.

8. A Special Case in Three Dimensions

In this section we handle the case $n = 3$ where (1) has k critical points satisfying (A4) or (D4). $\mathscr{C}_1$ will be assumed asymptotically stable and so $g(c) < 0$ for $c_1 < c < c_2$. Thus $\mathscr{C}_2$ is unstable and either $g(c) < 0$ for $c_2 < c < c_3$ or $g(c) > 0$ for $c_2 < c < c_3$. The latter will occur in the nondegenerate case. Here we prove that the orbit of each point in $\mathscr{H}$ is positively asymptotic to $\mathscr{C}_1$ or to an invariant set in $B(c_2, c_k)$. If $k = 3$ then orbits in $B(c_2, c_3)$ are asymptotic to $\mathscr{C}_2$ or $\mathscr{C}_3$ depending on the sign of g; and so for the three critical point case we have that each orbit is asymptotic to a critical point. Some of the topological arguments in this section are reminiscent of those we gave in [21] when analyzing the Griffith model.

First we show that each unstable critical point $\mathscr{C}_i$ has a 2-dimensional stable manifold M_i .An eigenvalue λ of $DF(\mathscr{C}_i)$ is a root of the polynomial:

$$\lambda^3 + (\alpha_1 + \alpha_2 + \alpha_3)\lambda^2 + (\alpha_1\alpha_2 + \alpha_1\alpha_3 + \alpha_2\alpha_3)\lambda + \alpha_1\alpha_2\alpha_3 - f'(c_i) = 0. \quad (12)$$

According to the Routh–Hurwitz criterion [14, p. 15], the number of roots of (12) with positive real parts is equal to the number of sign changes in the following sequence:

$$\left\{1, \sum_{k=1}^{3} \alpha_k, \left(\sum_{k=1}^{3} \alpha_k\right)^2\left(\sum_{k\neq j}^{3} \alpha_k\alpha_j\right) - \left(\sum_{k=1}^{3} \alpha_k\right) \times (\alpha_1\alpha_2\alpha_3 - f'(c_i)), \alpha_1\alpha_2\alpha_3 - f'(c_i)\right\}. \quad (13)$$

Each term in (13) is positive except possibly $\alpha_1\alpha_2\alpha_3 - f'(c_i)$. If $\mathscr{C}_i$ is degenerate then $\alpha_1\alpha_2\alpha_3 - f'(c_i) = 0$; so (12) has no roots with positive real parts. Hence the principal eigenvalue of a degenerate critical point is zero and M_i is 2-dimensional If $\mathscr{C}_i$ is nondegenerate then (13) has at most one sign change; so an unstable, nondegenerate $\mathscr{C}_i$ has a 2-dimensional stable manifold. We have proved:

Lemma 8.1. *Let $n = 3$ and $\mathscr{C}_i$ be an unstable critical point of* (1). *Then the stable manifold of $\mathscr{C}_i$ has codimension one. And thus the principal eigenvalue of a degenerate critical point is zero.*

An analogous result is true if $n = 4$ but Tyson and Othmer [24] have an example with $n = 5$ where an unstable critical point has a 3-dimensional unstable manifold.

Theorem 5.4 asserts that $B(c_1, c_k)$ is an attracting box. We divide $B(c_1, c_k)$ into eight subboxes by planes parallel to the coordinate planes and containing

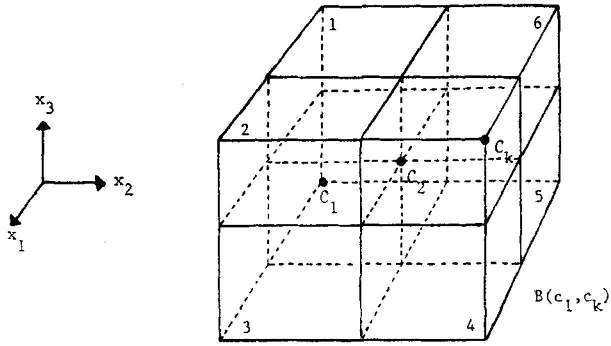

FIGURE 2

$\mathscr{C}_2$. $B(c_1, c_2)$ and $B(c_2, c_k)$ are two such boxes and the other six are defined as follows (see Fig. 2):

$$\mathrm{Box}(1) = \{x\colon c_1\phi_1 \leqslant x_1 \leqslant c_2\phi_1, c_1\phi_2 \leqslant x_2 \leqslant c_2\phi_2, c_2\phi_3 \leqslant x_3 \leqslant c_k\phi_3\},$$
$$\mathrm{Box}(2) = \{x\colon c_2\phi_1 \leqslant x_1 \leqslant c_k\phi_1, c_1\phi_2 \leqslant x_2 \leqslant c_2\phi_2, c_2\phi_3 \leqslant c_3 \leqslant c_k\phi_3\},$$
$$\mathrm{Box}(3) = \{x\colon c_2\phi_1 \leqslant x_1 \leqslant c_k\phi_1, c_1\phi_2 \leqslant x_2 \leqslant c_2\phi_2, c_1\phi_3 \leqslant x_3 \leqslant c_2\phi_3\},$$
$$\mathrm{Box}(4) = \{x\colon c_2\phi_1 \leqslant x_1 \leqslant c_k\phi_1, c_2\phi_2 \leqslant x_2 \leqslant c_k\phi_2, c_1\phi_3 \leqslant x_3 \leqslant c_2\phi_3\},$$
$$\mathrm{Box}(5) = \{x\colon c_1\phi_1 \leqslant x_1 \leqslant c_2\phi_1, c_2\phi_2 \leqslant x_2 \leqslant c_k\phi_2, c_1\phi_3 \leqslant x_3 \leqslant c_2\phi_3\},$$
$$\mathrm{Box}(6) = \{x\colon c_1\phi_1 \leqslant x_1 \leqslant c_2\phi_1, c_2\phi_2 \leqslant x_2 \leqslant c_k\phi_2, c_2\phi_3 \leqslant x_3 \leqslant c_k\phi_3\}.$$

In order to study the motion of orbits through these boxes, we need to establish some inequalities for the vector field F on the faces and interior of these boxes. First we find the direction of F on the planes parallel to the coordinate planes and containing $\mathscr{C}_2$. If $x_1 = c_2\phi_1$ then $F_1(x) = f(x_3) - \alpha_1 c_2\phi_1 = f(x_3) - \phi c_2$; so we have

$$\begin{aligned} &F_1(x) > 0 \text{ if } x_3 > c_2\phi_3 \text{ and } x_1 = c_2\phi_1, \\ &F_1(x) < 0 \text{ if } x_3 < c_2\phi_3 \text{ and } x_1 = c_2\phi_1. \end{aligned} \tag{14}$$

If $x_2 = c_2\phi_2$ then $F_2(x) = x_1 - \alpha_2 c_2\phi_2 = x_1 - c_2\phi_1$; so

$$\begin{aligned} &F_2(x) > 0 \text{ if } x_1 > c_2\phi_1 \text{ and } x_2 = c_2\phi_2, \\ &F_2(x) < 0 \text{ if } x_1 < c_2\phi_1 \text{ and } x_2 = c_2\phi_2. \end{aligned} \tag{15}$$

If $x_3 = c_2\phi_3$ then $F_3(x) = x_2 - \alpha_3 c_2\phi_3 = x_2 - c_2\phi_2$; so

$$\begin{aligned} &F_3(x) > 0 \text{ if } x_2 > c_2\phi_2 \text{ and } x_3 = c_2\phi_3, \\ &F_3(x) < 0 \text{ if } x_2 < c_2\phi_2 \text{ and } x_3 = c_2\phi_3. \end{aligned} \tag{16}$$

Similar computations for inside the boxes give

$$\begin{aligned} F_1(x) > 0 \text{ if } x_1 < c_2\phi_1 \text{ and } x_3 \geqslant c_2\phi_3 , \\ F_1(x) < 0 \text{ if } x_1 > c_2\phi_1 \text{ and } x_3 \leqslant c_2\phi_3 . \end{aligned} \tag{17}$$

$$\begin{aligned} F_2(x) > 0 \text{ if } x_2 < c_2\phi_2 \text{ and } x_1 \geqslant c_2\phi_1 , \\ F_2(x) < 0 \text{ if } x_2 > c_2\phi_2 \text{ and } x_1 \leqslant c_2\phi_1 . \end{aligned} \tag{18}$$

$$\begin{aligned} F_3(x) > 0 \text{ if } x_3 < c_2\phi_3 \text{ and } x_2 \geqslant c_2\phi_2 , \\ F_3(x) < 0 \text{ if } x_3 > c_2\phi_3 \text{ and } x_2 \leqslant c_2\phi_2 . \end{aligned} \tag{19}$$

From Theorem 5.4, we have $\operatorname{Int} B(c_1, c_2) \subset \operatorname{dom} \mathscr{C}_1$. And clearly $B(c_2, c_k)$ is positively invariant. Now we can discuss the orbits of boundary points of these two boxes.

LEMMA 8.2. $B(c_1, c_2)\backslash\mathscr{C}_2 \subset \operatorname{dom}(\mathscr{C}_1)$.

Proof. It follows from (14), (15), and (16) that the vector field points into $\operatorname{Int} B(c_1, c_2)$ on the open faces of $B(c_1, c_2)$. Also $\mathscr{C}_2$ is the only invariant set on the edges of $\partial B(c_1, c_2)$. Thus, by continuity, the orbit of each point on $\partial B(c_1, c_2)$ except $\mathscr{C}_2$ enters $\operatorname{Int} B(c_1, c_2)$ and so is asymptotic to $\mathscr{C}_1$.

LEMMA 8.3. $(B(c_2, c_k)\backslash(\mathscr{C}_2 \cup \mathscr{C}_k)) \cdot t \subset \operatorname{Int} B(c_2, c_k)$ *for all* $t > 0$.

Proof. Check the vector field on $\partial B(c_2, c_k)$ and argue as in Lemma 8.2.

LEMMA 8.4. $A \equiv B(c_1, c_2) \cup B(c_2, c_k)$ *is an attracting region.*

Proof. From Lemmas 8.2 and 8.3, the vector field on $\partial A\backslash(\mathscr{C}_1 \cup \mathscr{C}_2 \cup \mathscr{C}_k)$ is pointing into A and A is positively invariant. Recall that M_2 denotes the stable manifold of $\mathscr{C}_2$. Theorem 6.3 gives that $(M_2\backslash\mathscr{C}_2) \cap \operatorname{Int} B(c_1, c_k)$ belongs to the interior of $\bigcup_{i=1}^{6} \operatorname{Box}(i)$. And the unstable or center manifold N of C_2 belongs to the interior of A. N is unstable or center depending on the principal eigenvalue of $\exp(DF(\mathscr{C}_2))$. $\mathscr{C}_2$ is an isolated invariant set. Appealing to the theory of isolated invariant sets [1, 17] and to the Palis–Takens result [20] concerning the flow behavior near a critical point, we can choose a neighborhood of $\mathscr{C}_2$ such that each orbit in that neighborhood is either positively asymptotic to $\mathscr{C}_2$ or exits that neighborhood near N and hence in $\operatorname{Int} A$. Now, using the compactness of A, we can find a closed neighborhood of A whose ω-limit set is a subset of A. Thus A is an attracting region.

In $\operatorname{Box}(i)$, $i = 1, 2, \ldots, 6$, certain component functions are Lyapunov functions. It follows from (17) that the x_1-component function is increasing along orbits in Box(1). When an orbit exits Box(1), it must hit the open faces $x_1 = c_2\phi_1$ or $x_3 = c_2\phi_3$ or the edges belonging to A. Hence an orbit in Box(1) enters either A or

Box(2). Equation (19) implies that the x_3-component function is decreasing in Box (2). And it follows that an orbit in Box(2) enters A or Box(3). In Box(3), (18) gives that the x_2-component is increasing and orbits enter either A or Box(4). In Box(4), the x_1-component is decreasing and orbits enter either A or Box(5). In Box(5), the x_3-component is increasing and orbits enter either A or Box(6). In Box(6), the x_2-component is decreasing and orbits enter either A or Box(1). Thus an orbit in $B(c_1, c_k)$ either is asymptotic to an invariant set in A or spirals around the line $\mathscr{L}$ passing through the six numbered boxes in increasing numerical order modulo six. If there is a closed invariant set not contained in A then its orbits must spiral and it can be depicted as a cycle of six boxes. This spiraling behavior becomes much more complicated in higher dimensions. Even for $n = 4$, there are two intersecting cycles; and so the invariant set possibilities are increased. Such behavior has been observed in the negative feedback problem [6, 9, 11, 23] and other biochemical network problems [4, 5, 10].

The natural way to approach the unique cycle in 3-dimensions is to take a section for the flow and study the return map. As our section we choose the face shared by Box(1) and Box(2), i.e.,

$$\mathscr{S} \equiv \{x\colon x_1 = c_2\phi_1, c_1\phi_2 \leqslant x_2 \leqslant c_2\phi_2, c_2\phi_3 \leqslant x_3 \leqslant c_k\phi_3\}.$$

Let $\mathscr{P}$ denote the plane $x_1 = c_2\phi_1$. $\operatorname{Int}_{\mathscr{P}} \mathscr{S}$ denotes the interior of $\mathscr{S}$ with respect to $\mathscr{P}$. M_2 intersects $\mathscr{P}$ transversely. This is true because Lemma 6.2 implies transversality at $\mathscr{C}_2$ and Theorem 6.3 implies that M_2 intersects the line $\{x\colon x_1 = c_2\phi_1, x_3 = c_2\phi_3\}$ only at $\mathscr{C}_2$. Off this line F is transverse to $\mathscr{P}$ by (14). Thus M_2 intersects $\mathscr{P}$ in a 1-dimensional C^1 manifold [18]. Let $\mathscr{M}$ denote the connected component of $M_2 \cap \operatorname{Int}_{\mathscr{P}} \mathscr{S}$ with $\mathscr{C}_2 \subset \operatorname{Cl} \mathscr{M}$. Then $\mathscr{M}$ is a C^1 arc with $\mathscr{C}_2$ as an end point, see Figure 3. In Figure 3 the directed curves represent the motion of points under the return map.

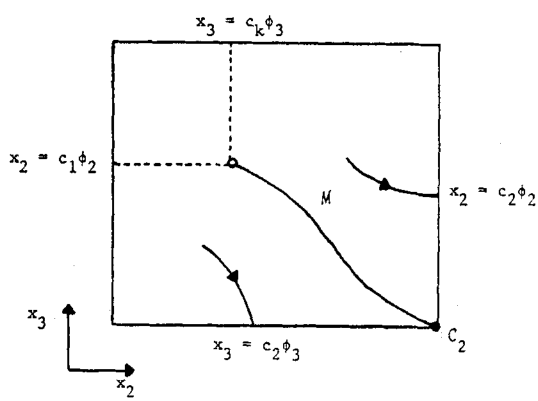

FIGURE 3

LEMMA 8.5. *Each point of $\mathscr{S}\backslash\mathscr{M}$ related to some point of $\mathscr{M}$ belongs to* dom A. *If the point is above $\mathscr{M}$ then its orbit is asymptotic to an invariant set in $B(c_2, c_k)$. If the point is below $\mathscr{M}$ then it belongs to* dom $\mathscr{C}_1$.

Proof. Take $w \in \mathscr{S}\backslash\mathscr{M}$ and suppose $w \leqslant u$ for some $u \in \mathscr{M}$. The point w is not in M_2 because w is related to u and no two points of M_2 are related. Since $u \cdot t \to \mathscr{C}_2$ as $t \to \infty$ and $w \cdot t \leqslant u \cdot t$, we have

$$\limsup_{t \to \infty} w_3(t) \leqslant c_2\phi_3. \tag{20}$$

Hence the orbit of w is not asymptotic to an invariant set in $B(c_2, c_k)\backslash\mathscr{C}_2$. The orbit of w may repeatedly return to $\mathscr{S}$ as t increases but ultimately it must cross the line $x_3 = c_2\phi_3$ into Int $B(c_1, c_2)$ or enter a small neighborhood of $\mathscr{C}_2$. In either case the orbit is asymptotic to $\mathscr{C}_1$. The Palis–Takens result implies that an orbit near $\mathscr{C}_2$ but below $\mathscr{M}$ leaves the neighborhood of $\mathscr{C}_2$ in Int $B(c_1, c_2)$ and so is asymptotic to $\mathscr{C}_1$.

A similar argument shows that points above $\mathscr{M}$ are asymptotic to an invariant set in $B(c_2, c_k)$.

We now show that $\mathscr{M}$ extends across Inttl $\mathscr{S}$ separating into two open sets. Note that, since $\mathscr{M}$ is a manifold, if $\mathscr{M}$ were to terminate in $\mathrm{Int}_{\mathscr{P}}\, \mathscr{S}$ then $\mathscr{M}$ would not contain its left end point, see Figure 3.

THEOREM 8.6. *$\mathscr{M}$ is a closed subset of* $\mathrm{Int}_{\mathscr{P}}\, \mathscr{S}$. *In fact, $\mathscr{M}$ must have a limit point of the edge $x_2 = c_1\phi_2$ or the edge $x_3 = c_k\phi_3$.*

Proof. From the preceding remark the only possibility we must eliminate is a point $z \notin \mathscr{M}$ which is an end point of $\mathscr{M}$ in $\mathrm{Int}_{\mathscr{P}}\, \mathscr{S}$, see Fig. 4. Such a z is not asymptotic to $\mathscr{C}_2$. Also z may not belong to dom A because then it would

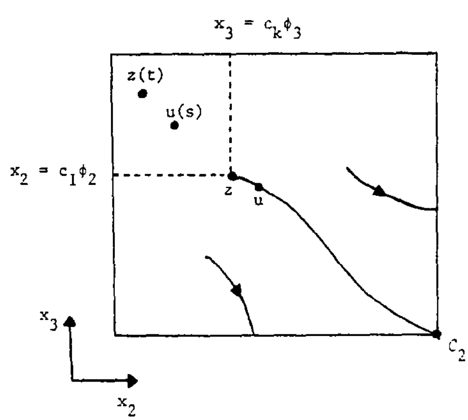

FIGURE 4

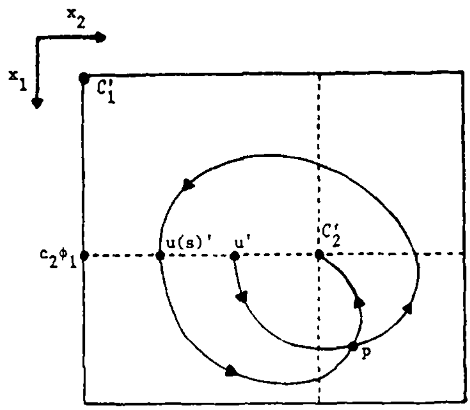

FIGURE 5

be asymptotic to $\mathscr{C}_1$ or an invariant set in Int $B(c_2, c_k)\backslash\mathscr{C}_2$. But this would force the orbits of points in $\mathscr{M}$ near z into $A\backslash\mathscr{C}_2$, which is impossible (Theorem 6.3). Thus the orbit of z must return to $\mathscr{S}$.

Suppose, for contradiction, that z is not a periodic point. Lemma 8.5 implies that the orbit of z returns to the closed upper left quadrant of $\mathscr{S}$, in Fig. 4 the region bounded by the dotted lines. By continuity and Theorem 6.3, there is a point $u \in \mathscr{M}$ which returns to $\mathscr{S}$ in the open upper left quadrant. The orbit of u is asymptotic to $\mathscr{C}_2$; so the x_1x_2-plane projection of this orbit must cross itself at some point p (see Fig. 5, where the primed notation denotes the x_1x_2-plane projection of the corresponding unprimed point). The orbit projection cannot cross the line $x_1 = c_2\phi_1$ in the negative x_1-direction between $c_2\phi_1$ and $\mathscr{C}_2$ because the vector field is pointing in the positive x_1-direction along that segment. The two points of the orbit of u which project onto p are related. But this contradicts Theorem 6.3. Hence z is a periodic point.

According to Proposition 2.1, for some $k \geqslant 2$, there is a k-dimensional C^1 manifold of points in Int $\mathscr{H}$ which are positively asymptotic to the orbit of z. This stable manifold meets $\text{Int}_{\mathscr{P}}\, \mathscr{S}$ in at least a 1-dimensional manifold. Lemma 8.5 confines this manifold to the upper left quadrant in Fig. 4. But this confinement contradicts the smoothness of this stable manifold. Hence the arc $\mathscr{M}$ cannot have an end point in $\text{Int}_{\mathscr{P}}\, \mathscr{S}$ and so it must extend across $\text{Int}_{\mathscr{P}}\, \mathscr{S}$ to the edges $x_2 = c_1\phi_2$ or $x_3 = c_k\phi_3$.

THEOREM 8.7. *Consider* (1) *with* $n = 3$. *Let* $\mathscr{C}_1$ *be asymptotically stable and let* $A = B(c_1, c_2) \cup B(c_2, c_k)$. *Then each point in* $\mathscr{H}$ *belongs to* dom A. *If the point is on* M_2 *then its orbit is positively asymptotic to* $\mathscr{C}_2$. *If the point is below* M_2 *then it belongs to* dom $\mathscr{C}_1$. *If the point is above* M_2 *then its orbit is positively asymptotic to an invariant set in* $B(c_2, c_k)$.

Proof. Take $p \in \mathscr{H}$. If the orbit of p is not asymptotic to $\mathscr{C}_1$ or $\mathscr{C}_k$ then it enters Int $B(c_1, c_k)$. In Int $B(c_1, c_k)$ the orbit of p belongs to dom A or spirals, repeatedly meeting $\mathrm{Int}_{\mathscr{P}} \mathscr{S}$. But Theorem 8.6 gives that each point of $\mathrm{Int}_{\mathscr{P}} \mathscr{S}$ is related to some point of $\mathscr{M}$. The result now follows from Lemma 8.5.

Theorem 8.7 is crucial to the induction arguments in the next two sections which prove the general 3-dimensional cases.

9. The Three-Dimensional Nondegenerate Case

As mentioned after Corollary 5.6, the nondegenerate case can be reduced to that of an odd number of critical points, $\mathscr{C}_1 < \mathscr{C}_2 < \cdots < \mathscr{C}_{2k-1}$, where $\theta < \mathscr{C}_1$. The odd subscripted critical points are asymptotically stable and the even subscripted are unstable. Lemma 8.1 asserts that each unstable critical point has a 2-dimensional stable manifold.

Theorem 9.1. *If* (1) *satisfies* (A4) *and* $n = 3$, *then the orbit of each point in* $\mathscr{H}$ *is positively asymptotic to some critical point. In fact, for* $j = 1,..., k-1$, *the stable manifold* M_{2j} *separates* dom $\mathscr{C}_{2j-1}$ *from* dom $\mathscr{C}_{2j+1}$.

Proof. We induct on k, the number of stable critical points. For $k = 1$ the critical point is a global attractor. The case $k = 2$ is a consequence of Theorem 8.7 because the orbit of each point in $B(c_2, c_3)$ except $\mathscr{C}_2$ is asymptotic to $\mathscr{C}_3$ since $g(c) > 0$ for $c_2 < c < c_3$.

As our induction hypothesis, we assume the result for the flow in an attracting box containing $k - 1$ stable critical points. This holds for $k = 2$ by virtue of Theorem 8.7. We now give the argument for k stable critical points.

The box $B(c_1, c_{2k-1})$ is an attracting box with $\mathscr{H} \subset$ dom $B(c_1, c_{2k-1})$. Theorem 8.7 gives that the orbit of each point in $\mathscr{H}$ is positively asymptotic to an invariant set in $B(c_1, c_2) \cup B(c_2, c_{2k-1})$. M_2 consists precisely of those orbits asymptotic to $\mathscr{C}_2$. If a point is below M_2 then it is in dom $\mathscr{C}_1$. If a point is above M_2 and not in dom $\mathscr{C}_{2k-1}$, then its orbit enters Int $B(c_2, c_{2k-1})$. But $B(c_3, c_{2k-1})$ is an attracting box with Int $B(c_2, c_{2k-1}) \subset$ dom $B(c_3, c_{2k-1})$, and $B(c_3, c_{2k-1})$ contains $k - 1$ stable critical points. By induction we know that the stable manifolds of the unstable critical points in $B(c_3, c_{2k-1})$ separate $B(c_3, c_{2k-1})$ into the domains of attraction of its stable critical points. Hence the proof is complete.

10. The Three-Dimensional Degenerate Case

Here we assume that (1) satisfies (D4) so any of the critical points may have a zero eigenvalue. However, Lemma 8.1 still gives that each unstable critical point has a 2-dimensional stable manifold. First we study the behavior when there are only two critical points.

LEMMA 10.1 *Let* (1) *satisfy* (D4) *and let* $n = 3$. *If* (1) *has exactly two critical points then the orbit of each point in* $\mathscr{H}$ *is positively asymptotic to one of these critical points. Also, the stable manifold of the unstable critical point is the boundary of the domain of attraction of the stable critical point.*

Proof. Since $g(0) \geqslant 0$ and $g(c) < 0$ for $c > c_2$, $B(c_1, c_2)$ is an attracting box with $\mathscr{H} \subset \operatorname{dom} B(c_1, c_2)$. For all $c, c_1 < c < c_2$, either $g(c) > 0$ or $g(c) < 0$.

Assume the former. Then $\mathscr{C}_2$ is asymptotically stable with $B(c_1, c_2)\backslash\mathscr{C}_1 \subset \operatorname{dom} \mathscr{C}_2$ and $\mathscr{C}_1$ is unstable. Hence each orbit in $\mathscr{H}$ is asymptotic to a critical point. The stable manifold M_1 of $\mathscr{C}_1$ is transverse to the line $\mathscr{L}$ and meets $B(c_1, c_2)$ only at $\mathscr{C}_1$, by Theorem 6.3. Analyzing the local behavior at $\mathscr{C}_1$, we see that the orbit of a point above M_1 leaves a neighborhood of $\mathscr{C}_1$ in $B(c_1, c_2)$ and hence is asymptotic to $\mathscr{C}_2$. And the orbit of a point below M_1 remains below M_1 and is asymptotic to $\mathscr{C}_1$. Using the fact that being related is positively invariant, we conclude that this local behavior is global.

If $g(c) < 0$ for $c_1 < c < c_2$ then the preceding argument with the roles of $\mathscr{C}_1$ and $\mathscr{C}_2$ interchanged gives the desired result.

THEOREM 10.2. *If* (1) *satisfies* (D4) *and* $n = 3$ *then the orbit of each point in* $\mathscr{H}$ *is positively asymptotic to a critical point. In addition, the stable manifold of an unstable critical point* $\mathscr{C}_i$ *separates* $\mathscr{H}$ *into regions or orbits positively asymptotic to* $\mathscr{C}_{i-1}$, $\mathscr{C}_i$, *or* $\mathscr{C}_{i+1}$ *depending on the sign of* g.

Proof. We induct on the number of critical points k. For $k = 1$, the critical point is a global attractor; and Lemma 10.1 handles the case $k = 2$. We assume the result for a positively invariant box containing $k - 1$ critical points, which is clear for 2 critical points from Lemma 10.1.

Suppose (1) has k critical points. Assume that $\mathscr{C}_1$ is asymptotically stable. Then $g(c) < 0$ for $c_1 < c < c_2$ so $\mathscr{C}_2$ is unstable. Theorem 8.7 applies to this situation giving that M_2 separates orbits asymptotic to $\mathscr{C}_1$ from orbits asymptotic to an invariant set in $B(c_2, c_k)$. But $B(c_2, c_k)$ is a positively invariant box with $k - 1$ critical points. Now using the induction hypothesis, we have the result.

If $\mathscr{C}_1$ is not asymptotically stable then $\mathscr{C}_1$ in unstable and $g(c) > 0$ for $c_1 < c < c_2$. It follows that $B(c_2, c_k)$ is an attracting box with $B(c_1, c_k)\backslash\mathscr{C}_1 \subset \operatorname{dom} B(c_2, c_k)$. The induction hypothesis implies the desired behavior in $B(c_2, c_k)$. And M_1 separates orbits asymptotic to $\mathscr{C}_1$ from orbits asymptotic to critical points in $B(c_2, c_k)$ as M_1 did in the proof of Lemma 10.1. Thus, the proof is complete.

11. Concluding Remarks

An obvious question to ask is whether the results of the last two sections remain valid if $n = 4$. If the stable manifolds of unstable critical points still have codimension one, they could separate $\mathscr{H}$. However, for $n = 3$, the flow through the six boxes, Box(i) $i = 1,..., 6$, is analyzed by taking one 2-face of a box as a cross section. For $n = 4$, the spiralling of orbits around $\mathscr{L}$ is more involved, with 14 instead of 6 boxes and two intersecting cycles of orbits. Here two adjoining 3-faces could be used as a cross section but the return map has yet to be analyzed. However, it appears that the conclusions of sections 9 and 10 will hold. For $n > 4$, the Tyson–Othmer example [24] indicates that the question of asymptotic behavior is much more complicated.

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